the polypeptide of any one of claims 61, 65, 67, 71-75 and 77] , operatively linked to a non-CRSP polypeptide.

C9 Cont

88. (Amended) A pharmaceutical composition comprising the polypeptide of any one of claims [61, 65, 67, 71-75 and 77] 62, 66, 68, 72-76 and 78 and a pharmaceutically acceptable carrier.

REMARKS

Claims 61-88 were pending in the instant application. In an effort to expedite prosecution of this application and in no way conceding the validity of the Examiner's position, Applicants have amended claims 62-65, 67, 69, 72-73, 79-85, and 87-88. No new claims have been added. No claims have been cancelled. Accordingly, claims 61-88 will be pending after entry of the instant amendment. For the Examiner's convenience, a copy of the claims after entry of the instant amendment are submitted herewith as APPENDIX A. Support for the claim amendments and new claims can be found throughout the specification and claims as originally filed.

The specification has been amended to remove blanks "_____" (*i.e.*, to supply the missing information), to remove reference to the hyperlink at page 28 and to correct other minor informalities. The title of the instant application has been amended to more clearly indicate the invention to which the claims are directed. No new matter has been added.

Information Disclosure Statement

At page 2 of the instant Office action, the Examiner states that "[t]here have been five Information Disclosure Statements (IDS) filed in the instant application: 26 October 1998, paper 2; 17 October 1998, paper 3; 29 October 1998, paper 7; 17 December 1999, paper 8 and 20 December 1999, paper 9." The Examiner further states that "[p]apers 7 and 8 are duplicates of papers 2 and 3, respectively will be placed in the file, but not considered further". Applicant would like to clarify for the record that only three Information Disclosure Statements (IDSs)

have been filed in the instant application: a first mailed by Applicant on October 26, 1998, received by the U.S.P.T.O. October 29, 1998; a second mailed December 10, 1998, received December 17, 1998; and a third mailed December 14, 1999, received December 20, 1999. Applicant is unaware of the source of duplication but suggests that paper nos. 2, 8 and 9 correspond to the three IDSs filed in the instant case. The Examiner has considered papers 2, 3 and 9. As papers 8 and 3 are believed to be identical (citing a single reference, PCT application no. WO 98/27932), Applicant presumes that the publications and information of which he and his attorney are aware are adequately of record in the case.

With respect to at least some of the publications which Applicant has made of record, in particular the GenBank records and BLAST search results submitted by Applicant, it is noted that the Examiner has not considered the references because, according to the Examiner "[t]hese citations are not in conformance with MPEP 609 because, at the very least, they do not contain dates and/or authors". The Examiner further states that "given the extremely high number of citations for consideration (close to 150 such citations), Applicant should indicate the relevance of each of the references (for example, because the actual alignments form the BLASTN searches are not provided, the relevance of the citations is unknown to the Examiner)". While the Examiner has considered the balance of the references cited by Applicant, the Examiner has not yet considered references AM-AR, BA-BT, and CA-CS cited in paper no.2 or references AG-AR, BA-BR, CA-CT, DA-DN cited in paper no.9. In order to assist the Examiner in understanding the relevence of the above-enumerated references in order that she may consider them, Applicant submits herewith replacement PTO-1449 Forms corresponding to those submitted with paper nos. 2 and 9, the replacements listing a "publication date" for at least the GenBank records included among references AM-AR, BA-BT, and CA-CS (paper no.2) and references AG-AR, BA-BR, CA-CT, DA-DN (paper no.9). Applicant invites the Examiner's attention to the fact that the "publication date" listed for each of references AM-AR, BA-BT, and CA-CS (paper no.2) and references AJ-AR, BA-BR, CA-CT, DA-DN (paper no.9), which are

printouts of electronic GenBank database records, corresponds to a date appearing on a printout of the record indicating ***either*** the date the record was first made publicly available ***or*** the date the record was subsequently revised. In the case of revised records, Applicant further invites the Examiner's attention to the fact that earlier versions of such electronic records may have been available prior to the "publication date" appearing on the printed record and listed in the replacement PTO-1449 Forms submitted herewith. However, Applicant is unaware of the content of such earlier versions, and/or of the nature of any data added or revised with each revision of such electronic records.

"Authors" have not been provided for the GenBank records cited in the replacement PTO-1449 Forms submitted herewith as Applicant is unaware of the identity of any particular *person* who may have authored the GenBank records cited. The Examiner is invited to look at the printed copies of the GenBank records provided with paper nos. 2 and 9, in particular, to the REFERENCE field of the database record, for the source of the information (*e.g.*, printed publications, direct submissions, or a combination thereof) used to create a particular record. Moreover, neither publication dates nor authors have been listed for the three BLAST reports cited as referenced AG-AI in paper no.9 as these are are not "printed publications" having an "author" or "publication date". Rather, these BLAST reports were generated by the Assignee and have been provided to assist the Examiner in understanding the relevence of the GenBank records cited in paper nos. 2 and 9, as it is from these BLAST reports that Applicant became aware of many of the GenBank references cited in paper nos. 2 and 9. Each BLAST report includes alignments of the CRSP-2 nucleic acid or amino acid sequence of the invention with various "hits" from the GenBank EST, non-redundant nucleic acid or non-redundant protein database. Applicant became aware of additional GenBank records cited in paper nos. 2 and 9 by performing BLAST searches using CRSP-1, CRSP-3, CRSP-4 and CRSP-N sequences described in the instant specification and have been included in the Information Disclosure Statements because these other CRSP family members share significant homology with CRSP-2 (as claimed

in the instant application). Applicant suggests that the above information should adequately assist the Examiner in considering references AM-AR, BA-BT, and CA-CS (paper no.2) and references AG-AR, BA-BR, CA-CT, DA-DN (paper no.9) and respectfully requests that the enumerated referenced now be considered.

Claim Objections

The Examiner has objected to the numbering of new claims 61-87 added by Applicant's amendment filed December 14, 1999. The Examiner has renumbered claims 61-87 added by an amendment filed December 14, 1999 as claims 62-88 in accordance with 37 CFR 1.126. Applicant has reviewed the claims and corrected the dependencies of the pending claims in accordance with the new numbering. The Examiner has also requested that Applicant clarify the status of originally-filed claim 61. Applicant has reviewed the prosecution history of the instant application and notes the following for the record. In an Office communication dated September 28, 1999 (Paper No. 6), the Examiner listed claims 1-60 as pending in the application and subjected said claims to a restriction requirement. In Applicant's amendment filed December 14, 1999, Group III (claims 20-31) were elected for prosecution in the present application. Non-elected claims 1-20 and 32-60 as well as elected claims 20-31 were canceled from the application. New claims numbered 61-87 were added (now correctly numbered as claims 62-88). Applicant notes that originally-filed claim 61 was not listed by the Examiner in the "Office Action Summary" (Form PTO-326) accompanying Paper No. 6 or discussed in the detailed action attached thereto. Originally-filed claim 61 was not subject to restriction requirement in Paper No. 6. By contrast, in the instant action (Paper No. 12) claim 61 is listed in the "Office Action Summary" and discussed in the detailed action attached thereto. It would appear that the Examiner has chosen to examine claim 61 in conjunction with the subject matter of elected Group III. Accordingly, Applicant will assume that originally-filed claim 61 has been included with the elected Group III subject matter unless indicated otherwise by the Examiner.

The Examiner objects to claims 74 and 75 as allegedly being duplicates of one another. Applicant respectfully traverses. Claim 74 is directed to an isolated polypeptide that includes an amino acid sequence which is encoded by a nucleic acid molecule which hybridizes to the complement of the nucleic acid molecule consisting of SEQ ID NO:4 or 6 under conditions of *incubation at 45 ℃ in 6.0 X SSC followed by washing in 0.2 X SSC, 0.1% SDS at 50 ℃*. Claim 75 is directed to an isolated polypeptide that includes an amino acid sequence which is encoded by a nucleic acid molecule which hybridizes to the complement of the nucleic acid molecule consisting of SEQ ID NO:4 or 6 under conditions of *incubation at 45 ℃ in 6.0 X SSC followed by washing in 0.2 X SSC, 0.1% SDS at 65 ℃*. It is Applicant's position that claims 74 and 75, differ in scope, such scope being distinguished by the recitation of different stringency conditions in claims 74 and 75 (*i.e.*, washing at 50°C versus 65°C). In view of the clear difference in scope between the subject matter of claims 74 and 75, Applicant respectfully requests reconsideration of the objection to claims 74 and 75 as being "duplicates of one another".

Rejection of claims 61-88 Under 35 U.S.C. §101 and 35 U.S.C. §112, first paragraph

Claims 61-88 stand rejected under 35 U.S.C. 101 because, according to the Examiner, "the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility". In particular, it is the Examiner's position that "[t]he instant disclosure does not provide specific functions for the CRSP-2 polypeptide, nor does it teach phenotypes which occur as a result of the over expression CRSP-2, nor does it teach phenotypes which occur as a result of under or no expression of CRSP-2, nor does the disclosure set forth any specific diseases or conditions which are related to the over or under expression of CRSP-2. The specification does not teach a single, specific and substantial utility for any CRSP protein/polypeptide, including the instantly claimed CRSP-2". Claims 61-88 also stand rejected under 35 U.S.C. 112, first paragraph because, according to the Examiner, "since the claimed invention is not supported by either a specific and substantial asserted utility or a well established

utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention". Applicant traverses.

The present invention features a novel family of secreted signaling factor proteins, the human CRSP proteins. Four family members have been identified and are described in the instant specification, namely human CRSP-1, CRSP-2, CRSP-3 and CRSP-4 (a murine homologue for CRSP-1 is also described). Applicant has described the chemical, physical and biological properties of the CRSP family of proteins in the instant specification, at least for example, at page 7, line 20 through page 9, line 30; at page 10, line 3 through page 12, line 14; and in Figure 7 which depicts the the relationship between the CRSP proteins of the instant invention and the biological and functional domains of the human CRSPs. The chemical, physical and biological properties of the individual CRSP protein are further taught in the instant specification at least for example, at page 12, line 15 through page 13, line 12 as well as in Examples 1-2. Briefly, Applicants have identified a family of novel secreted soluble signaling proteins involved in modulation of development and differentiation. That the CRSP proteins are secreted soluble signaling factors is evidenced, at least in part, by the fact that the proteins include hydrophobic signal peptides, are devoid of additional transmembrane domains, and include abundant and strongly conserved cysteine residues with potential for disulfide cross-linking. CRSP family members are characterized, in particular, by a conserved cysteine-rich region which includes at least two cysteine-rich domains. Working examples demonstrate that an exemplary family member, CRSP-1, is a secreted factor. By performing structural analysis and sequence comparison of the CRSP family members, Applicant has further identified signal sequences in additional family members, evidencing that the proteins comprise a family of secreted proteins.

The specification further teaches how to recombinantly produce the CRSP proteins of the present invention at least for example, at page 35, line 16 through page 39, line 4. Applicant further asserts that the CRSP proteins of the present invention can be used as modulators of

differentiation and/or development, can be used in screening assays to identify compounds (*e.g.*, small molecule compounds) useful as modulators of development and/or differentiation, as well as to generate CRSP-specific antibodies useful for similar purposes. Applicant asserts that each of these proposed utilities are specific and substantial utilities, meeting the requisites of 35 U.S.C. 101.

That the asserted utilities are specific is clear from the fact that the general class of molecules to which the claimed CRSP proteins belong, *i.e.*, isolated protein molecules, do not posess the specific utility ascribed to the CRSP proteins of the present invention. In particular, all recombinant proteins are not capable of being used to modulate differentiation and/or development or as targets in screens to identify such modulators. As support of Applicant's stated biological function and specific proposed utilities, Applicant draws the Examiner's attention to the fact that Xenopus and mouse proteins having homology to CRSP-3 have been reported as being important in development (see *e.g.*, References AG, BS and BT cited in the IDS filed October 26, 1998, describing such related proteins and their function in head induction). Applicant notes that these related Xenopus and mouse proteins and their role in modulating development was described prior to Applicant's filing date (see Appendix B which includes earlier printouts of the electronic GenBank records having Accession Nos. AF03043 and AF030433, in particular, the titles and annottions of the appended database records). A chicken cDNA related to CRSP-1 has been reported to be important in differentiation (*e.g.*, expression of this related cDNA correlates with the terminally differentiated state in chick lens fibers, see Reference AL cited in an IDS filed by Applicant on October 26, 1998). These CRSP proteins, as well as the instant claimed CRSP proteins are each part of a family of proteins sharing chemical, physical and biological properties as described in detail in the instant specificaiton. Although Applicant is not relying on the cited publications to establish an activity and/or utility for the claimed nucleic acid molecules, Applicant brings these publications to the Examiner's attention to further *evidence the credibility of Applicant's prior assertions of utility.*

Likewise, Applicant draws the Examiner's attention to the Krupnik *et al.* reference (Reference DQ cited in the IDS filed by Applicant on December 14, 1999) discussed at pages 5-6 of the office action dated March 13, 2000. In particuler, Applicants points the Examiner to page 311 of Krupnik *et al.* which demonstrate that hDkk-4 (the equivalent of CRSP-2) modulates head induction based on experiments in which the authors (which include the instant inventor) injected hDkk-4 mRNAs into developing *Xenopus* embryos and determines that the injected hDkk4 was capable of inhibiting Wnt-induced axis duplication. Contrary to the Examiner's assertion that a role for the CRSP proteins was mere "hypothesized" in Krupnik *et al.*, Applicant respectfully submits that Krupnik *et al.* experimentally confirms Applicant's asserted activity of the CRSP proteins of the present invention as secreted modulators of development.

Moreover, the utilities asserted by Applicant are not "throw away" utilities (*e.g.*, use as a food supplement or cosmetic additive). As the Examiner is aware, an applicant must provide only one credible assertion of specific utility for any claimed invention to satisfy the utility requirement. The instant application teaches a specific biological role for the CRSP proteins as well as setting forth their significance. No evidence has been made of record that Applicant's assertions regarding activities and/or utilities of the CRSP secreted factors as modulators of differentiation and/or development would not be considered credible to one of skill in the art. Moreover, it Applicant's position that the Examiner's statements of record fail to constitute a reasoned explanation as to why the utilities asserted by Applicant would not be specific and substantial. Reconsideration under 37 CFR 1.111 is requested.

Rejection of Claims 62-69, 72, 73, 79-85, 87 and 88 Under 35 U.S.C. 112, Second Paragraph

Claims 62-69, 72, 73, 79-85, 87 and 88 stand rejected under 35 U.S.C. 112, second paragraph, as allegedly being "indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention".

In particular, the Examiner states that "[c]laims 62 and 63 are indefinite because it is not clear if the claims are drawn to polypeptide that is either at least 80 or 90% identical to amino acid sequence of SEQ ID NO:5 or at least 80 or 90% identical to the amino acid sequence of SEQ ID NO:5 less the first nineteen amino acids or if the claims are drawn to a polypeptide that is either at least 80 or 90% identical to the amino acid sequence of SEQ ID NO:5 or is simply SEQ ID NO:5 less the first nineteen amino acids. Claims 62 and 63 have been amended to use Markush language as suggested by the Examiner. Applicant submits that amended claims 62 and 63 distinctly claim and particularly point out the subject matter which Applicant regards as the invention and respectfully requests reconsideration and withdrawal of the rejection of claims 62 and 63.

Claims 64-69, 84-85 and 88 stand rejected because, according to the Examiner, "the specification defines a "cysteine-rich region" as a protein domain with about 120-200 amino acid residues of which about 10-30 are cysteine residues. Because the specification defines 'a cysteine-rich region' as a 'cysteine-rich domain', it is not clear what the distinction is between the two terms, thus it is not clear what the distinction is between that which is claimed in claims 64-69, 84 and 85 and dependent claim 88". Applicant traverses.

Claims 64, 66, 67 and 85 are drawn to isolated polypeptides having at least 90% identity to the amino acid sequence of SEQ ID NO:5 (or to the amino acid sequence of SEQ ID NO:5 without amino acids 1 to 19) which include a cysteine-rich region. Claims 65, 68, 69, 84 are drawn to isolated polypeptides having at least 90% identity to the amino acid sequence of SEQ ID NO:5 (or to the amino acid sequence of SEQ ID NO:5 without amino acids 1 to 19) which include a cysteine-rich domain. The instant specification defines a cysteine-rich *region* as "a protein domain having an amino acid sequence of about 120-200, preferably about 130-190, more preferably about 140-180 amino acid residues, and even more preferably at least about 135-175 amino acids of which at least about 10-30, preferably about 15-20, and more preferably about 16, 17, 18, or 19 of the amino acids are cysteine residues" (see *e.g.*, page 7, lines 33-37).

Examplary cysteine-rich ***regions*** are taught in at least four CRSP family members at least, for example, at page 8, lines 1-10.

The instant specification further defines a cysteine-rich ***domain*** as "a protein domain having an amino acid sequence of about 30-100 amino acids, preferably about 35-95 amino acids, more preferably about 40-90 amino acids, more preferably about 45-85 amino acids, even more preferably about 50-80 amino acids, and even more preferably about 55-75, 60-70, or 65 amino acids, of which at least about 3-20, preferably about 5-15, or more preferably about 6, 7, 8, 9, 10, 11, or 12 amino acids are cysteine residues" (see *e.g.*, page 8, lines 12-18). The instant specification further teaches that preferred CRSP proteins have two cysteine-rich domains within a cysteine-rich region (see *e.g.*, page 8, lines 18-19). Cysteine-rich domains (included within cysteine-rich regions) in at least four CRSP family members are further exemplified, for example, at page 8, lines 19-37. The instant specification clearly distinguishes between the terms "cysteine-rich region" and "cysteine-rich domain", the latter being smaller in size, containing fewer cysteine residues, being included within larger cysteine-rich regions, etc. As the specification clearly distinguishes between the two terms, Applicant submits that the subject matter of claims 64, 66, 67, 85 (which recite "cysteine-rich regions") and claims 65, 68, 69, 84 (which recite "cysteine-rich domains") is clearly distinguishable and respectfully requests reconsideration and withdrawal of the rejection of claims 64-69, 84 and 85 and 88 under 35 U.S.C. 112, second paragraph.

Claims 72 and 73 have been rejected over the recitation of the phrase "or a complement thereof" because, according to the Examiner, it is not clear to what the recited phrase refers (*e.g.*, a nucleic acid or polypeptide) and a complement of SEQ ID NO:4 or SEQ ID NO:6 cannot encode the claimed polypeptide. Applicant traverses.

In order to expedite prosecution of the instant application and without acquiescing to the Examiner's rejections, claims 72 and 73 have been amended to remove the language "or a

complement thereof". Accordingly, Applicant respectfully requests reconsideration and withdrawal of the rejection of claims 72 and 73 under 35 U.S.C. 112, second paragraph.

Claims 79-83 stand rejected over the recitation of the phrase "the fragment comprises" because, according to the Examiner "there is no antecedent basis for this recitation in claim 78 from which these claims depend". Claims 79-83 have been amended. Amended claims 79-83 no longer recite the objected to language. Applicant submits that claim 78 presently provides proper antecedent basis for amended claims 79-83 and accordingly, requests reconsideration and withdrawal of the rejection of claims 72 and 73 under 35 U.S.C. 112, second paragraph.

Claim 87 stands rejected over the recitation of the phrase "a polypeptide which is heterologous to the polypeptide of ...". According to the Examiner, "recitation of the phrase 'a polypeptide which is heterologous to the polypeptide of ...' renders the claim indefinite because it is not clear what is encompassed by the claim. Applicant traverses. It is Applicant's position that the ordinarily skilled artisan would know what is meant by the terms "heterologous" and/or "endogenous" as these terms are routinely used to describe fusion proteins and have a well accepted meaning in the art. The instant specification further exemplifies such fusion proteins containing CRSP polypeptide sequences operatively linked to heterologous sequences (*e.g.*, fusion proteins having CRSP sequences linked to a signal sequence from another protein, linked to GST sequences, linked to Ig sequences, and the like) (see *e.g.*, page 28, line 11 through page 29, line 26 of the instant specification). However, in order to expedite prosecution of the instant application, claim 87 has been amended to recite that the claimed fusion proteins comprise the polypeptide of any one of claims 62, 66, 68, 72-76 and 78, "operatively linked to a non-CRSP polypeptide" (*i.e.*, language supported, for example, by claim 30 as originally filed). In view of the above remarks and amendments, Applicant submits that the metes and bounds of claim 87 are clearly set forth. Reconsideration and withdrawal of the rejection are requested.

CONCLUSION

In view of the foregoing amendments and following remarks, it is respectfully submitted that the application is in condition for allowance. If the Examiner has any questions or believes that a telephone conversation with Applicant's Attorney would be helpful in expediting allowance of this application, the Examiner is invited to call the undersigned at (617) 227-7400.

Respectfully submitted,

LAHIVE & COCKFIELD, LLP

By: _____

Debra J. Milasincic
Registration No. P46,931
28 State Street
Boston, MA 02109
(617) 227-7400
(617) 742-4214

Date: August 14, 2000

APPENDIX A

61. A method for identifying a compound that modulates the activity of a CRSP protein, comprising:

a. providing a indicator composition comprising a protein having CRSP-2 activity;

b. contacting the indicator composition with a test compound; and

c. determining the effect of the test compound on CRSP-2 activity in the indicator composition to thereby identify a compound that modulates the activity of an CRSP-2 protein.

62. (Amended) An isolated polypeptide comprising an amino acid sequence at least 80% identical to an amino acid sequence selected from the group consisting of the amino acid sequence of SEQ ID NO:5 and the amino acid sequence of SEQ ID NO:5 without amino acids 1 to 19.

63. (Amended) The polypeptide of claim 62, which comprises an amino acid sequence which is at least 90% identical to an amino acid sequence selected from the group consisting of the amino acid sequence of SEQ ID NO:5 and the amino acid sequence of SEQ ID NO:5 without amino acids 1 to 19.

64. (Amended) The polypeptide of claim 62, wherein the amino acid sequence comprises a cysteine-rich region.

65. (Amended) The polypeptide of claim 62, wherein the amino acid sequence comprises a cysteine-rich domain.

66. An isolated polypeptide comprising a cysteine-rich region which is at least 80% identical to amino acids 41 to 218 of SEQ ID NO:5.

67. (Amended) The polypeptide of claim 66, wherein the cysteine-rich region comprises amino acids 41 to 218 of SEQ ID NO:5.

68. An isolated polypeptide comprising a cysteine rich domain which is at least 80% identical to amino acids 41 to 90 of SEQ ID NO:5 or to amino acids 138 to 218 of SEQ ID NO:5.

69. (Amended) The polypeptide of claim 68, wherein the cysteine-rich domain comprises amino acids 41 to 90 of SEQ ID NO:5 or amino acids 138 to 218 of SEQ ID NO:5.

70. An isolated polypeptide comprising the amino acid sequence of SEQ ID NO:5.

71. An isolated polypeptide comprising the amino acid sequence of SEQ ID NO:5 without amino acids 1 to 19.

72. (Amended) An isolated polypeptide encoded by a nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO:4.

73. (Amended) An isolated polypeptide encoded by a nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO:6.

74. An isolated polypeptide comprising an amino acid sequence which is encoded by a nucleic acid molecule which hybridizes to the complement of the nucleic acid molecule consisting of SEQ ID NO:4 or 6 under conditions of incubation at 45°C in 6.0 X SSC followed by washing in 0.2 X SSC, 0.1% SDS at 50°C.

75. An isolated polypeptide comprising an amino acid sequence which is encoded by a nucleic acid molecule which hybridizes to the complement of the nucleic acid molecule consisting of SEQ ID NO:4 or 6 under conditions of incubation at 45°C in 6.0 X SSC followed by washing in 0.2 X SSC, 0.1% SDS at 65°C.

76. An isolated polypeptide comprising an amino acid sequence which is encoded by a nucleic acid molecule comprising a nucleotide sequence which is at least 80% identical to the nucleotide sequence consisting of SEQ ID NO:6.

77. An isolated polypeptide comprising an amino acid sequence which is encoded by a nucleic acid molecule comprising a nucleotide sequence which is at least 90% identical to the nucleotide sequence consisting of SEQ ID NO:6.

78. An isolated polypeptide comprising at least 10 consecutive amino acids of the amino acid sequence of SEQ ID NO:5.

79. (Amended) The polypeptide of claim 78, which comprises at least 25 consecutive amino acids of SEQ ID NO:5.

80. (Amended) The polypeptide of claim 79, which comprises at least 50 consecutive amino acids of SEQ ID NO:5.

81. (Amended) The polypeptide of claim 80, which comprises at least 100 consecutive amino acids of SEQ ID NO:5.

82. (Amended) The polypeptide of claim 81, which comprises a cysteine-rich domain of SEQ ID NO:5.

83. (Amended) The polypeptide of claim 80, which comprises a cysteine-rich region of SEQ ID NO:5.

84. (Amended) The polypeptide of claim 82, wherein the cysteine-rich domain comprises amino acids 41 to 90 of SEQ ID NO:5 or amino acids 138 to 218 of SEQ ID NO:5.

85. (Amended) The polypeptide of claim 81, wherein the cysteine-rich region comprises amino acids 41 to 218 of SEQ ID NO:5.

86. An isolated polypeptide consisting of the amino acid sequence selected from the group consisting of SEQ ID NO:5 and SEQ ID NO:5 without amino acids 1 to 19.

87. (Amended) A fusion polypeptide comprising the polypeptide of any one of claims 62, 66, 68, 72-76 and 78, operatively linked to a non-CRSP polypeptide.

88. (Amended) A pharmaceutical composition comprising the polypeptide of any one of claims 62, 66, 68, 72-76 and 78 and a pharmaceutically acceptable carrier.

APPENDIX B-1

NCBI Entrez **Protein QUERY** BLAST Entrez ?

Other Formats: FASTA | Graphic

Links: DNA | Related Sequences

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DEFINITION  mdkk-1.
ACCESSION   2736292
PID         g2736292
DBSOURCE    GENBANK: locus AF030433, accession AF030433
KEYWORDS    .
SOURCE      house mouse.
  ORGANISM  Mus musculus
            Eukaryotae; Metazoa; Chordata; Vertebrata; Mammalia; Eutheria;
            Rodentia; Sciurognathi; Muridae; Murinae; Mus.
REFERENCE   1  (residues 1 to 272)
  AUTHORS   Glinka,A., Wu,W., Delius,H., Monaghan,P., Blumenstock,C. and
            Niehrs,C.
  TITLE     Dickkopf-1 is a member of a new family of secreted proteins and
            functions in head induction
  JOURNAL   Nature (1998) In press
REFERENCE   2  (residues 1 to 272)
  AUTHORS   Glinka,A., Wu,W., Delius,H., Monaghan,P., Blumenstock,C. and
            Niehrs,C.
  TITLE     Direct Submission
  JOURNAL   Submitted (21-OCT-1997) Division of Molecular Embryology, Division
            of Applied Tumorvirology, Division of Molecular Biology of the Cell
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Save the above report in Macintosh ▼ Text ▼ format.

APPENDIX B-2

NCBI Entrez **Protein QUERY** BLAST Entrez ?

Other Formats: FASTA | Graphic

Links: DNA | Related Sequences

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ACCESSION   2736294
PID         g2736294
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KEYWORDS    .
SOURCE      African clawed frog.
  ORGANISM  Xenopus laevis
            Eukaryotae; Metazoa; Chordata; Vertebrata; Amphibia; Batrachia;
            Anura; Mesobatrachia; Pipoidea; Pipidae; Xenopodinae; Xenopus.
REFERENCE   1  (residues 1 to 259)
  AUTHORS   Glinka,A., WU,W., Delius,H., Monaghan,P., Blumenstock,C. and
            Niehrs,C.
  TITLE     Dickkopf-1 is a member of a new family of secreted proteins and
            functions in head induction
  JOURNAL   Nature (1998) In press
REFERENCE   2  (residues 1 to 259)
  AUTHORS   Glinka,A., Wu,W., Delius,H., Monaghan,P., Blumenstock,C. and
            Niehrs,C.
  TITLE     Direct Submission
  JOURNAL   Submitted (21-OCT-1997) Division of Molecular Embryology, Division
            of Applied Tumorvirology, Division of Molecular Biology of the Cell
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       61 ankyqplday plysctеddd caldefchss rngnslvcla crkrrkrclr damcctgnyc
      121 sngicvpveq dqerfqhqgy leetilenyn nadhatmdth sklttspsgm qpfkgrdgdv
      181 clrstdcapg lccarhfwsk ickpvldegq vctkhrrkgs hgleifqrch cgaglscrlq
      241 kgefttvpkt srlhtcqrh
//
```

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